Characterization of axon guidance cue sensitivity of human embryonic stem cell-derived dopaminergic neurons.

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Public Summary:
Neuron replacement therapy for Parkinson's disease involves the transplant of stem cell-derived neurons into the brain. Neurons are the cells of the brain that form the interconnected circuitry. Connectivity is normally established during fetal development and there is very little information available about how stem cell-derived neurons will connect when placed into the adult brain long after development is complete. Neurons connect to each other by growing thin appendages called axons. These wire-like axons establish interconnected networks of neurons that provide the normal functions of the nervous system. Parkinson's disease selectively kills "dopaminergic" neurons and the goal in neuron replacement therapy is to transplant new dopaminergic neurons that will connect properly to augment function. As a first step in understanding how connectivity is established by dopaminergic neurons during development, the experiments in this publication first identify two molecules that influence the direction that axons grow. Using dopaminergic neurons isolated from the developing rat brain, we were able to show that a molecule called "netrin" strongly attracts axons while a molecule called "slit" repels axons from dopaminergic neurons. We were also able to show that human dopaminergic neurons made from embryonic stem cells respond in the same way, thus confirming that stem cell-derived neurons do behave similarly to neurons isolated directly from the developing brain. Ongoing research is identifying additional guidance molecules that influence dopaminergic neuron connectivity and with this information in hand, we are examining the signals present in the adult brain to determine if the connectivity of transplanted dopaminergic neurons can be enhanced by manipulating guidance signals in models of Parkinson's disease.

Scientific Abstract:
Dopaminergic neurons derived from human embryonic stem cells will be useful in future transplantation studies of Parkinson's disease patients. As newly generated neurons must integrate and reconnect with host cells, the ability of hESC-derived neurons to respond to axon guidance cues will be critical. Both Netrin-1 and Slit-2 guide rodent embryonic dopaminergic (DA) neurons in vitro and in vivo, but very little is known about the response of hESC-derived DA neurons to any axonal guidance cues. Here we examined the ability of Netrin-1 and Slit-2 to affect human ESC DA axons in vitro. hESC DA neurons mature over time in culture with the developmental profile of DA neurons in vivo, including expression of the DA neuron markers FoxA2, En-1 and Nurr-1, and receptors for both Netrin and Slit. hESC DA neurons respond to exogenous Netrin-1 and Slit-2, showing an increased responsiveness to Netrin-1 as the neurons mature in culture. These responses were maintained in the presence of pro-inflammatory cytokines that might be encountered in the diseased brain. These studies are the first to evaluate and confirm that suitably matured human ES-derived DA neurons can respond appropriately to axon guidance cues.